Comments by Sauerhoff & Associates and corresponding replies by OEHHA

Section 1 – Summary - Comments and Responses

Comment 1: The second paragraph of the caprolactam TSD contains the following quote. "High doses administered orally to pregnant rats caused fetal weight loss." This statement is irrelevant and misleading in the Summary and should be deleted. OEHHA does not use decreased fetal weights from a rat reproduction study as a basis for calculating the proposed REL or CREL. Including the statement about fetal weight loss in the Summary directs attention to fetal effects in rats that have no bearing on the proposed REL or CREL.

Response 1: The summary paragraph is merely a very brief description of the known toxic responses to caprolactam exposure in both humans and animals. As noted in the first paragraph of the summary section, SB 25 mandates that we explicitly consider all possible differential effects on the health of infants, children and other sensitive subpopulations. Thus, we must consider and report any data we find that examines caprolactam toxicity in the young. Currently, the best data for the effects of caprolactam exposure in the young are from animal studies in which pregnant rats were given caprolactam by gavage. It was not our intent to mislead or direct attention from the basis of the RELs developed. We note in the paragraph that high doses are needed to produce the effect of reduced fetal weight, which implies this particular outcome is not as sensitive or a more potent effect then the eye and upper respiratory effects we summarized in the sentence previous to one that describes the known developmental effects of caprolactam. However, we will re-word the summary paragraph to more strongly emphasize that the RELs are based on upper respiratory effects in humans (acute REL) and animals (8-hr and chronic RELs).

Section 1.1 – Acute REL Summary – Comments and Responses

Comment 2: The conversion between $\mu g/m^3$ and ppb appears incorrect. The value of 50 $\mu g/m^3$ converts to 11 ppb and not 3 ppb as shown in the TSD.

Response 2: We thank the reviewers for pointing out this discrepancy. Conversion of acute REL of 50 $\mu g/m^3$ to ppb using the formula 4.63 mg/m^3 = 1 ppm (or conversely, 4.63 $\mu g/m^3$ = 1 ppb) as shown in Section 2 does indeed result in 11 ppb. Rounded to one significant figure, as the authors have done in their human exposure study (i.e., 0.5 mg/m3), would have resulted in an acute REL of 10 ppb (1×10^1 ppb). Note that the acute REL has since been revised.

Comment 3: Is the Acute 1-hour REL for a vapor exposure only? The caprolactam vapor pressure (0.001 mm at 68ºF; 0.0021 mm Hg at 77ºF) is considered low. The 8-Hour REL and Chronic REL are both for aerosol exposure. The inconsistency between vapor and aerosol is confusing and needs to be clarified.

Response 3: We are simply describing the form of caprolactam that was used in the specific studies that we based the RELs on. Caprolactam is a semi-volatile compound. In other words, it can exist in both solid and gaseous form, but one form may predominate depending on the temperature, pressure and humidity conditions. As noted in Section 2, the saturated vapor concentration of caprolactam at 25ºC is about 13 mg/m^3. A large proportion of caprolactam will condense out of the air from gaseous to aerosol/solid form when an air concentration of about 13

mg/m^3 is reached. Since the human acute exposure study by Ziegler et al. (2008) used a concentration of 5 mg/m^3 as the high exposure, with a temperature at 22ºC and a humidity at a relatively low 60%, the form of caprolactam during the exposures was predominantly as a vapor (i.e., gas phase).

In the animal exposure study by Reinhold et al. (1998), caprolactam concentrations were 24, 70 and 234 mg/m^3, with a chamber temperature of 25 ºC and a relative humidity of 50%. As noted by the authors of this study, because the concentration was above the saturated vapor pressure, the predominant form of caprolactam the rats were exposed to was as an aerosol.

A comprehensive published analysis of the potency of each form of caprolactam has not been performed. However, as we note in Section 5.1, the industrial study by Ferguson and Wheeler (1973) suggest that high humidity increases the threshold for sensory irritation of caprolactam. What does not appear to be in question is that regardless of the form of caprolactam, the toxic endpoint of sensory irritation is the same. We will add a sentence that notes no studies have been conducted comparing the potency of gaseous or aerosol forms of caprolactam, but that both forms are expected to result in similar toxicological effects.

Comment 4: It is quite important to state whether the "Critical Effect(s)" is from human studies or those conducted in laboratory animals. Further, it is of equal importance to define whether the "Critical Effect" is systemic or local (e.g., irritation). For caprolactam, the "Critical Effect" is local. Further comments will be offered in Section 8.1 relative to the specific proposed acute 1-hour REL in the TSD.

Response 4: We will note in Section 1.1 that the critical effect described was due to human exposure. However, section 1.1 is only a very brief summary and it should be self-evident from the listed hazard index targets of respiratory system and eyes that caprolactam's effects are designed to protect against the local action of the chemical where it comes into contact with the body. As noted in the summary in section 5.1 and in 1.1, the acute endpoint for the initial proposed acute REL was due to increased total symptom and complaint score. These include eye, nose and throat irritation but also skin irritation, smell and taste perception, blurred vision, headache, and feelings of dizziness or weakness and other questions about general feelings of well-being. None of these effects by themselves were statistically significantly increased except for odor. But together, a statistically significant increase ($p < 0.05$) was noted at 5 mg/m^3. The methodology used in the design of the human exposure study is described in Section 5.1.

We have revised the acute REL and the new REL is based on nose and throat irritation in workers.

Section 1.2 – 8-Hour REL Summary – Comments and Responses

Comment 5: Is the Acute REL for an aerosol exposure only? The proposed Acute REL is for vapor exposure. What is the rationale for developing a REL for vapor or aerosol? Please refer to Section 1.2 for comments on vapor and/or aerosol REL values and Critical Effects. Further comments will be offered in Section 8.2 relative to the specific proposed 8-Hour REL in the TSD.

Response 5: Refer to Response 3 regarding the form of caprolactam used for acute and subchronic exposures. In addition, the Commenter appears to be confused about the definition of the 8-hour REL. An 8-hour REL is meant to protect against repeated daily exposures of 8 hours over long periods of time, not unlike operations of many facilities that may emit pollutants off-site only during working hours. In this respect, the 13-week subchronic animal study (6 hours/day, 5 days/week for 13 weeks) used as the basis of the 8-hour REL most closely reflects the purpose of the 8-hour REL in which the injury accumulated during the intermittent exposures. The human acute exposure study (6 hours per exposure at three different caprolactam exposure concentrations and one control exposure that were randomized over 4 consecutive days) was designed to study each individual level of exposure (i.e., resembling more of a recurrent acute exposure) and does not reflect the repeated exposure scenario of long-term daily 8-hour exposure for which the 8-hour REL is designed.

Section 1.3 – Chronic REL Summary – Comments and Responses

Comment 6: Is the proposed Chronic REL for an aerosol exposure only? The Acute REL is for vapor exposure. What is the rationale for developing a REL for vapor or aerosol?

Response 6: Please refer to Response 3 regarding the form of caprolactam used in the studies examined by OEHHA, which is dependent largely on whether the exposure concentrations were above (aerosol form will predominate) or below (vapor form will predominate) the saturated vapor concentration of caprolactam. We will add clarifying remarks about what form of caprolactam humans may be exposed to at the REL levels developed by OEHHA.

Section 2 – Physical and Chemical Properties - Comments and Responses

Comment 7: The vapor pressure for caprolactam is considered extremely low (Rheinhold et al., 1998; Toxicological Sciences: Vol. 44, pp. 197-205). The fact that caprolactam's vapor pressure is considered extremely low adds important perspective for this compound and that the vapor pressure is extremely low needs to be added to the caprolactam TSD. While the caprolactam vapor pressure of 0.0021 mm Hg at 25ºC (77ºF) is included in the TSD, the more widely accepted caprolactam vapor pressure value of 0.001 mm Hg at 20ºC (68ºF) should be added.

Response 7: It should be self-evident that a vapor pressure of 0.0021 mmHg @ 25ºC listed in Section 2 would be considered relatively low compared to other chemicals that OEHHA developed RELs for. However, we also point the Commenter to Section 3, paragraph 2, where Ferguson and Wheeler (1973) in their industrial study characterized caprolactam as a solid at room temperatures, but with a significant vapor pressure. Listing vapor pressures for chemicals in the range of room temperatures at both 20 and 25ºC is common. We have added the vapor pressure of 0.001 mm Hg at 20ºC (68ºF) as suggested by the Commenter. We also added to Section 2 that caprolactam is considered a semi-volatile compound to emphasize the relatively low vapor pressure.

Section 3 - Occurrence and Major Uses – Comments and Responses

Comment 8: The Hodgson et al., 2004 study measured average caprolactam concentrations in classrooms over an 8-hour school day. The average value was 22.2 µg/m^3 with a range of values from 10.6 µg/m^3 to 30.1 µg/m^3. These average values to which children were exposed is 13X-to-38X greater than the chronic REL, respectively, as proposed in the caprolactam TSD. Importantly, the Hodgson et al., 2004 report makes no mention of any symptoms or detection of odor as a result of exposures as high as 30.1 µg/m^3. At a minimum, an exposure of 22.2 µg/m^3-to-30.1 µg/m^3 is a no-adverse effect level (NOAEL) for children. Apparently, the findings from the Hodgson et al., 2004 study were ignored or not considered in the context of OEHHA establishing REL values.

Response 8: The Hodgson et al., (2004) study was primarily designed to determine and mitigate volatile organic chemical (VOC) concentrations, including caprolactam, in new relocatable school classrooms. The study was not designed to assess toxicological effects in the exposed children and nowhere in the study do the authors discuss signs of toxicological exposure in the exposed children. Specifically, the purpose of the study was to: (1) determine if indoor air concentrations of VOCs of concern were reduced through the process devised by the authors for interior material selection, and (2) determine if indoor VOC concentrations in the new classrooms were predicted with reasonable accuracy from the results of the laboratory study of material VOC emissions.

Because the Hodgson et al. study did not examine or discuss any effects from exposure to VOCs including caprolactam, it cannot be used as the basis of the RELs.

Section 5.1 - Acute Toxicity to Humans - Comments and Responses

Comment 9: The first sentence in this section reads as follows. “No studies were located regards effects of human exposure to finished products emitting caprolactam in indoor air environments.” This sentence excludes occupational exposures. The OEHHA draft caprolactam TSD contradicts itself. In fact, Section 3 refers to the Hodgson et al., 2004 study in which children were exposed to caprolactam vapors for over 8 weeks. The study makes no mention of symptoms or detection of odor during the 8-week period. Certainly, the Hodgson et al., 2004 study qualifies as a study of human exposure to finished products emitting caprolactam. Why this study was ignored by OEHHA is not evident. The Hodgson et al., 2004 study makes an important contribution to our understanding of the absence of caprolactam-related health effects and must be included as OEHHA revises its caprolactam risk assessment.

Response 9: The first sentence of Section 5.1 is in recognition that no published studies have been conducted examining toxicological effects of caprolactam from finished products that contain the chemical (e. g. finished Nylon 6 carpets). We will clarify this sentence to specify this detail. Occupational studies looked at caprolactam monomer exposures prior to formation of Nylon 6 fibers and during the polymerization process to form the fibers. However, OEHHA would certainly welcome additional well conducted chamber studies to shed further light on the toxicology of caprolactam emitted from finished Nylon 6 products.

Regarding Hodgson et al. (2004), as stated above in Response 8 this study was designed to only examine emission and concentrations of caprolactam and other VOCs in new relocatable classrooms from various building products. It did not assess caprolactam-related health effects in the exposed children and teachers and was never intended to do so. Thus, it cannot be used for caprolactam REL derivation.

Comment 10: The second sentence in paragraph 1 refers to occupational exposure. In the occupational setting, caprolactam is known to cause dermal, eye, and upper respiratory tract irritation. OEHHA claims that clear dose-response is lacking. Without question, there is a dose response relationship to chemical irritants. The lack of a dose response relationship in the two studies cited by OEHHA ([Kelman 1986; Human Toxicology: Vol. 5, pp. 57-59]; [Billmaier et al., 1992; EPA/OTS Doc #86-920001041]) cannot be used by OEHHA to claim lack of dose response and drive REL values to unjustifiably low levels.

Response10: The second sentence referred to by the Commenter was not meant to imply that irritants in general or caprolactam altogether lacks an irritant dose-response relationship. The sentence in question refers to the difficulty by OEHHA to discern any clearly written dose-response information from the industrial studies, including Kelman (1986) and Billmaier et al. (1992). For example, probably the best occupational dose-response data discussed in Section 5.1 comes from another industrial study by Ferguson and Wheeler (1973) in which 5 unacclimated workers were briefly exposed to 10, 14, 25, and 104 ppm (46, 65, 116, and 482 mg/m^3) caprolactam at the industrial facility. Most or all reported nasal and throat irritation at all levels, but no further information is supplied to determine a dose-response relationship and the specific exposure duration is not reported. However, OEHHA revised the acute REL derivation based on the sensory irritation LOAEL from the Ferguson and Wheeler study. Support for the basis of the acute REL is provided in the REL derivation section.

Comment 11: Zeigler et al., 2008 employed objective measures of eye irritation including blink frequency recordings, digital slit lamp photography to examine conjunctival hyperemia, and a standardized ophthalmologic grading scale to measure ocular redness. In addition, Zeigler et al., 2008 utilized anterior rhinomanometry to compare nasal resistance before and after exposure. Based on the objective measures described, irritation of the eyes and upper airways were not identified. In other words, no ocular or upper respiratory health effects were elicited in subjects exposed to caprolactam concentrations up to 5 mg/m^3 for 6 hours/day for four days. A subjective rating of discomfort ("not at all" to "somewhat") was noted at 5 mg/m^3 while subjective detection of malodor was reported at 0.15 mg/m^3. The absence of ocular and upper respiratory irritation determined by quantifiable and objective measures negates the subjective reporting by study subjects. The absence of ocular and upper respiratory tract irritation leads directly to the conclusion that the caprolactam concentration of 5 mg/m^3 is the no-adverse effect level (NOAEL). Subjective reporting of "somewhat" discomfort cannot be considered an adverse effect as indicated in the caprolactam TSD (page 5, paragraph 4, sentence 1). The NOAEL from this 4-day study in humans is 6,250X the chronic REL proposed by OEHHA.

Response 11: Although statistical significance at $p < 0.05$ did not occur for the objective measures of nasal resistance and eye blink frequency, it should be noted that the authors observed a trend towards greater nasal resistance and eye blink as caprolactam concentration

increased. The specific p values were not included by the authors. An increasing trend for subjective eye and nose irritation was also observed but also did not reach statistical significance at $p < 0.05$. When 29 acute symptoms are combined into a total daily score, a statistically significant increase is observed at 5 mg/m^3. OEHHA initially used this total score relevant for REL derivation because the total symptom score includes all measures that can be directly attributed to the acute sensory irritation and feelings of well-being. Nevertheless, OEHHA acknowledges that the highest exposure concentration of 5 mg/m^3 in the Ziegler study indicates it is a free-standing NOAEL for human sensory irritation. Thus, we have revised our acute REL and are now basing it on the Wheeler and Ferguson (1973) study.

As noted in the OEHHA Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (2008) on pages 36 and 37, the basis for an acute REL includes mild adverse effects such as sensory or subjective effects. Clearly, a mild adverse effect occurred among volunteers when one considers the statistically significantly increased total symptom and complaint score at 5 mg/m^3 caprolactam, and a trend with increasing dose for nasal resistance and eye blink. However, we have contacted the authors (Dr. Zeigler or Dr. Triebig) to discuss their findings as they relate to OEHHA's acute RELs, and to determine if odor nuisance alone was responsible for the statistically significantly increased total symptom score at 5.0 mg/m^3. We have revised the acute REL derivation based on the LOAEL for sensory irritation from Ferguson and Wheeler.

Finally, the Commenter's statement that the NOAEL from the Ziegler et al. 4-day study in humans is 6,250 times the chronic REL proposed by OEHHA is irrelevant. As noted in Response 5 above, the Ziegler et al. study examined the acute effects of caprolactam and cannot be used as the basis of chronic or 8-hour RELs. The adverse effect was mild enough over 4 days of daily exposure (one of which was a control exposure) that the effect resembles more of a recurrent acute exposure over a 4-day span. The chronic and 8-hour RELs are based on long-term continuous or intermittent exposures that cover a significant portion of a lifespan, often characterized as about 12 percent or more of life expectancy. These procedures are specified in the Revised Air Toxics Hot Spots Program Technical Support Document for the Derivation of Noncancer Reference Exposure Levels and RELs for Six Chemicals (OEHHA, 2008) and are applied to the RELs that we develop for any chemical.

Section 6.3 - Chronic Toxicity in Experimental Animals - Comments and Responses

Comment 12: Table 2 in the OEHHA caprolactam TSD provides the incidences of microscopic findings in the nasoturbinates and larynx in the Reinhold et al., 1998 study. Table 2 from the caprolactam TSD is reproduced below. The data for males (10) and females (10) are combined. The total number of rats observed (20) is the denominator in each cell. The numerator represents the number of rats with the specific endpoint or finding.

Table 2. Incidences of microscopic findings of nasoturbinal and larynx lesions in the 13-week caprolactam exposure study in rats (Reinhold et al., 1998)

Endpoint[a]	Exposure Group (mg/m^3)			
	0	24	70	243
Nasal respiratory mucosa[b]	0/20	4/20	8/20	12/20
Nasal respiratory mucosa at 4-week recovery[b]	0/20	0/20	6/20	5/20
Nasal olfactory mucosa[c]	0/20	2/20	8/20	17/20
Nasal olfactory mucosa at 4-week recovery[c]	2/20	2/20	7/20	19/20
Laryngeal tissue[d]	0/20	5/20	12/20	20/20
Laryngeal tissue at 4-week recovery[d]	0/20	0/20	1/20	3/20
Keratinized metaplastic epithelium of larynx[e]	0/20	0/20	0/20	5/20

[a] Nasal and larynx endpoints were categorically graded by a pathologist, on a scale from lowest to highest severity, as minimal, slight, moderate, or moderately severe. Statistical analysis of the pathology findings was not presented.
[b] Goblet cell hypertrophy/hyperplasia - moderate changes only; minimal and slight changes were at background levels
[c] Intracytoplasmic eosinophilic material – including slight, moderate, and moderately severe changes
[d] Squamous/squamoid, metaplasia/hyperplasia – minimal and slight changes only at terminal sacrifice, and minimal changes only at 4-week recovery
[e] Minimal changes only

I have summarized the same data as actually shown in the Reinhold et al., 1998 report with one important exception. All grades including minimal, slight, moderate and moderately severe changes are shown. Please note the table below.

Endpoint[a]	**Exposure Group (mg/m^3)**			
	0	**24**	**70**	**243**
Nasal respiratory mucosa[b]	19/20	20/20	19/20	20/20
Nasal respiratory mucosa at 4-week recovery[b]	19/20	18/20	18/20	19/20
Nasal olfactory mucosa[c]	17/20	15/20	18/20	20/20
Nasal olfactory mucosa at 4-week recovery[c]	17/20	19/20	17/20	20/20
Laryngeal tissue[d]	0/20	5/20	12/20	20/20
Laryngeal tissue at 4-week recovery[d]	0/20	0/20	1/20	3/20
Keratinized metaplastic epithelium of the larynx[e]	0/20	0/20	0/20	5/20
Larynx tissue at 4-week recovery	0/20	0/20	1/20	3/20

a Nasal and larynx endpoints were categorically graded by a pathologist, on a scale from lowest to highest severity, as minimal, slight, moderate, or moderately severe. Statistical analysis of the pathology findings was not presented: b Goblet cell hypertrophy/hyperplasia – all changes: c Intracytoplasmic eosinophilic material – all changes: d Squamous/squamoid, metaplasia/hyperplasia – all changes: e Minimal changes only

The table shown directly above captures the data taken directly from Reinhold et al., 1998 Tables 3, 4, and 5. The differences between the two tables above (Table 2 from the OEHHA TSD and the table I prepared directly from the Reinhold et al., 1998 study) are striking. The table as shown in the OEHHA caprolactam TSD (Table 2) does not capture all the data and is misleading regarding the interpretation of the data. One has to wonder whether this manipulation of the data was purposeful or inadvertent. At a minimum, if OEHHA is going to show data from a published study and use that data as a pivotal finding in their calculation of a REL, then any discrepancies between the OEHHA table and the table as generated by the study authors (Reinhold et al., 1998) must be clearly elucidated.

Response 12: As noted in Table 3 of the Draft Caprolactam REL document, minimal and slight changes of nasal respiratory mucosa and minimal changes of the olfactory mucosa were at background levels, and thus, not included in the Table. In other words, minimal and/or slight changes occurred in nearly all control animals indicating that as the animal ages, a low grade inflammatory change in the mucosal tissue occurs naturally in this species of rat. OEHHA had no intent to mislead the reader. The intent of Table 3 was to highlight the exacerbation by caprolactam of the naturally-occurring low grade inflammatory reaction in the rat nasal mucosa to higher grades of damage. Text will be included in the Section 6.3 to better highlight this point.

Also, note that no background laryngeal mucosal inflammatory injury occurred in the aging rats among control animals. Thus, the minimal and slight changes that occurred in laryngeal mucosa in exposed animals were entirely due to caprolactam exposure. Using the benchmark concentration approach as shown in Table 4 of the draft REL document, it is interesting to note that almost the same point of departure was found in both nasal respiratory tissue (4 mg/m^3) and laryngeal tissue (3 mg/m^3) when considering only the grade level changes resulting from caprolactam exposure.

Comment 13: Rheinhold et al., 1998 concluded that the NOAEL was 70 mg/m^3 based on upper respiratory effects with 243 mg/m^3 representing a no-observed effect level (NOEL) for systemic toxicity, neurotoxicity, and lower respiratory tract effects. In addition, importantly, there were no ophthalmic findings attributable to caprolactam. It is also highly likely that systemic exposures to caprolactam were higher than the actual values reported. Rats were exposed to caprolactam in a whole-body exposure chamber. Rats continually self-groom and very likely ingested caprolactam on their fur.

Response 13: As noted in Section 8.2 of the Draft Caprolactam REL Document, Reinhold et al. considered laryngeal keratinization of the metaplastic epithelium to be the primary adverse effect, resulting in a LOAEL of 243 mg/m^3 and a NOAEL of 70 mg/m^3. However, OEHHA notes in the same Section that under our REL Guidelines respiratory adverse effects also include mild irritant/inflammatory changes, such as occurred in the upper respiratory tract mucosa of the nasal and laryngeal tissue. By these guidelines, OEHHA observed a LOAEL at the lowest concentration of 24 mg/m^3, and no NOAEL. We agree with the Commenter that no apparent systemic, neurotoxic or ophthalmic changes were reported at the caprolactam exposures used in the study. The caprolactam-related injury was confined to the tissue lining of the upper respiratory system, which is not considered a systemic-type injury.

Comment 14: For REL calculations as shown in TSD Sections 8.2 and 8.3, OEHHA uses the 3 mg/m^3 value. OEHHA has completely disregarded the NOAEL of 70 mg/m^3 as reported by Rheinhold et al., 1998 in their peer-reviewed published manuscript. Instead, OEHHA has employed a 23.3X factor, without justification, claiming that 3 mg/m^3 is the point of departure for calculations of the proposed 8-hour REL and chronic REL for caprolactam.

Response 14: As noted in Response 13 above, Reinhold et al. had different criteria in deciding what the NOAEL is. Reinhold et al. considered keratinization of the metaplastic epithelium in

the larynx to be the adverse effect on which they based their determination of the NOAEL. They considered the exacerbation of mucosal inflammatory changes occurring in all exposed groups to be an adaptive response to the respiratory irritant effects of caprolactam, and therefore, not relevant for determination of the NOAEL. These types of mild inflammatory changes are primary endpoints of toxicity as indicated in the Revised Air Toxics Hot Spots Program Technical Support Document for the Derivation of Noncancer Reference Exposure Levels and RELs for Six Chemicals.

Because the exacerbation of mucosal inflammatory changes shows a dose-response effect and occurred at all dose levels, no NOAEL was observed for this endpoint. Thus, we applied established benchmark dose procedures published by U.S. EPA to determine the exposure benchmark concentration for a 5% response rate. As noted in Section 6.3 of the Caprolactam REL Document, the BMCL05 (the 95% lower confidence interval at the 5% response rate) is considered to be a concentration associated with a low level of response used as a point of departure for REL derivation.

In addition, overlooked by the Commenter and Reinhold et al. is the dose-responsive increase in clear nasal discharge and moist rales observed in exposed animals beginning at about 2 weeks of exposure. Here is a clear indicator of irritant injury to the respiratory tract that was induced after about 2 weeks of intermittent exposure to caprolactam. The eventual production of such an injury with continued exposure to an irritant chemical is a hallmark of chronic exposure. It is unfortunate that the authors did not attempt to better quantitate this toxic response for their report.

Section 8.1 - Derivation of the Acute Air Reference Exposure Level - Comments and Responses

Comment 15: OEHHA uses the Zeigler et al., 2008 study as a basis for calculating the proposed acute 1-hour REL. OEHHA misinterprets the results of the Zeigler et al., 2008 study claiming the NOAEL is 0.5 mg/m^3 wherein the study authors report a NOAEL of 5 mg/m^3 -- a difference of 10X. In addition, OEHHA does not make any adjustment for the fact that the Zeigler et al., 2008 study exposed subjects to caprolactam for 6 hours a day for 4 days. Without question, the caprolactam NOAEL for a 1 hour human inhalation study conducted for 1 day only would be significantly higher than that identified (5 mg/m^3) by Zeigler et al., 2008. OEHHA makes no mention of this important consideration.

Response 15: Please refer to Response 11 regarding OEHHAs' interpretation of the findings by Zeigler et al. and OEHHA selection of the NOAEL. Also note that in the conclusions by Ziegler et al., 0.5 mg/m^3 is indicated to be the No Observed Effect Level (NOEL), whereas 5 mg/m^3 is said to the No Observed Adverse Effect Level (NOAEL). OEHHA considers the combined 29 acute symptoms score finding of a statistically significant increase at 5 mg/m^3 to be relevant for REL derivation because the total symptom score includes all measures that can be directly attributed to the acute sensory irritation and feeling of well-being. Rather than a NOEL, we consider this result to be a NOAEL (0.5 mg/m^3) using the OEHHA methodology for REL development.

Regarding the comment that a 1 hour REL should be higher given that the study conducted exposures 6 hours/day over 4 days (with 1 day actually a control exposure), Figure 5 in Ziegler et al. should help the Commenter understand the dynamics of concentration vs. duration for sensory irritants. A statistically significant increase in total symptom score was noted immediately after entering the chamber containing 5 mg/m^3 caprolactam. The score did not change after the first hour, third hour or sixth hour of exposure. In addition, the slight increase in scores at the lower caprolactam concentrations also did not change throughout the exposure period either. This is a common finding in acute exposure studies of chemosensory irritants; they tend to be primarily concentration dependent and exposure-duration (or dose) independent. Once the concentration of a chemosensory irritant reaches a level causing sensory irritation, the magnitude of the effect will not increase or decrease significantly for the remaining duration of the acute exposure, unless there is a moderating adaptive effect or irritation of tissues unrelated to sensory irritation. For this reason, no time adjustment was used in deriving the initially proposed acute REL. Note that we have revised the acute REL and it is now based on sensory irritation in the Wheeler and Ferguson study.

Comment 16: Adding insult to injury, OEHHA employs a toxicodynamics uncertainty factor of 10X. OEHHA states that no data were located to ascertain if children or other groups might be differentially susceptible during acute exposure to caprolactam. Therefore, an uncertainty factor of 10X (toxicodynamics uncertainty factor as noted in previous sentence) is applied to address the potential variation in the intraspecies toxicodynamics response, including child/adult asthmatic responses to an irritant. OEHHA need not look any further than their own caprolactam TSD document and the references they cited in which adult and children studies have been conducted over weeks at concentrations higher than 0.5 mg/m^3 in the absence of any mention of asthma induced by caprolactam. Thus, the proposed acute 1-hour caprolactam REL is unsubstantiated, based on misinterpretation of data and ignores data contained within their own TSD document.

Response 16: None of the references OEHHA has cited in the Caprolactam REL Document includes any toxicological information or discussion of susceptible individuals (i.e., asthmatics or other sensitive individuals) exposed to caprolactam. As noted in Response 8 above, the Hodgson et al. (2004) study of caprolactam air levels and other VOCs in occupied school classrooms did not measure any health parameters or conduct a toxicological risk assessment of the exposed children because this was not the purpose of the study. Additionally, it is unknown if any of the children involved were asthmatics. Because the RELs are based on respiratory tract chemosensory effects (acute REL) and respiratory tract injury (8-hour and chronic RELs), and no data exists to support a lack of exacerbation of respiratory effects in sensitive individuals exposed, an intraspecies uncertainty factor = 10 is normally applied to protect susceptible individuals including children with asthma (see page 48 of the TSD for the Derivation of Noncancer Reference Exposure Levels, OEHHA (2008)).

Comment 17: Governmental and other Authorities have developed and adopted workplace exposure limits for caprolactam. The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted an 8-hour time-weighted average (TWA) exposure limit of 5 mg/m^3. The National Institute of Occupational Safety and Health (NIOSH) has adopted a 1 mg/m^3 8-hour TWA and short-term exposure limit (STEL)/Ceiling limit of 3 mg/m^3 for

caprolactam dust. The German DFG MAK has adopted an 8-hour TWA of 5 mg/m^3. NIOSH has also adopted a caprolactam vapor 8-hour TWA of 1 mg/m^3 (equivalent to 0.22 ppm) and STEL/Ceiling limit of 3 mg/m^3 (equivalent to 0.66 ppm). These 8-hour limits are for durations of exposure 8X longer than the 1-hour REL proposed by OEHHA. The caprolactam TSD document makes no mention of these important Authority values and that recognized exposure standards are from 20X to 100X higher for exposures that are 8-times longer in duration than the proposed caprolactam acute 1-hour REL.

Response 17: It is almost always the case that occupational limits for chemicals are higher than OEHHA Reference Exposure Levels and other standards designed to protect the general public. Occupational exposure guidelines are designed to protect healthy adult workers, and not the sensitive subpopulations in the general population such as children, the sick, pregnant women, the elderly, or those with genetically predetermined sensitivities. Occupational values are not derived on a consistent basis, and include risk management and feasibility considerations specific to industrial facilities. In many cases the values may not even prevent adverse health effects among workers and sometimes do not incorporate recently available data. It is generally accepted that workers in the workplace will assume a greater risk because of their economic interest, than would be appropriate for the general public. OEHHA's RELs do not apply to the workplace. See pages 80-81 and 93 of the TSD for the Derivation of Noncancer Reference Exposure Levels (OEHHA, 2008) for more information concerning the inadequacy of using occupational values for OEHHA RELs.

Section 8.2 - Derivation of the 8-Hour Air Reference Exposure Level – Comments and Responses

Comment 18: Inexplicably, OEHHA has chosen the 13-week rat subchronic toxicity study (Rheinhold et al., 1998) as a point of departure for calculating the proposed caprolactam 8-hour REL. There is no rationale whatsoever for OEHHA to ignore the wealth of human data regarding what are essentially acute exposures. Using a 13-week subchronic inhalation study in the rat as a basis upon which to calculate a safe level of exposure for an up to 8-hour human exposure is completely unscientific, unjustified and without support in the scientific literature.

Response 18: The Commenter appears to be under the incorrect assumption that the 8-Hour RELs are designed only for single 8-hour exposures. Eight-hour RELs are concentrations at or below which adverse effects are not likely to occur in the general human population with repeated intermittent exposures of eight hours per day, up to 7 days per week. As such, they resemble chronic, long-term exposures rather than one-time acute exposures.

The human data for long-term exposure to caprolactam is inadequate for the basis of 8-hour and chronic RELs. Occupational studies of caprolactam exposure relied on a few analyses of concentrations in specific facility locations to estimate historical levels of caprolactam at the facility, and did not provide reliable worker histories of personal exposure. In addition, aside from sensory irritation resulting from occasional brief exposures to high levels of caprolactam, inadequate or non-existent data is supplied in the occupational studies to assess long-term injury from caprolactam exposure. Thus, the best available data from which to estimate 8-hour and chronic RELs is the Reinhold et al. (1998) subchronic exposure study in rats.

Comment 19: OEHHA has misinterpreted the 13-week subchronic toxicity study data including the NOAEL (see Section 6.3).

Response 19: This comment appears to be related to the presentation of nasal mucosal findings in Table 3 of the Caprolactam REL Document in which low-grade background changes to nasal mucosa were not included in the Table. As noted in Response 12 above, the intent of Table 3 was to highlight the exacerbation by caprolactam of the naturally-occurring low grade inflammatory reaction in the rat nasal mucosa to higher grades of damage. Text has been included in the Section 6.3 to better explain this point.

Comment 20: Rather than use the NOAEL of 70 mg/m^3, OEHHA employs the BMCL05 dose of caprolactam (3 mg/m^3) for the start of the 8-hour REL calculation. Use of the BMCL05 introduces an incorrect and unjustified safety factor of 23.3X.

Response 20: The identification of the LOAEL at the lowest exposure concentration, the lack of a NOAEL for the purposes of REL development, and the use the benchmark concentration methodology to derive the REL, was already covered in Response 14 above.

Comment 21: OEHHA adjusted the systemic dose of caprolactam in the rat subchronic inhalation study based on respiration rate in rats compared to humans. This approach, conceivably, may be applicable when systemic toxicity is the key endpoint in a rat study and the dose is then extrapolated to humans. However, OEHHA established the key endpoint as upper respiratory tract irritation. Upper respiratory tract or eye irritation is dependent on concentration and not systemic dose. Thus, lowering the point of departure concentration from 3 mg/m^3 to 0.2443 mg/m^3 introduced another incorrect and unjustified safety factor of 12.3X.

Response 21: The Commenter appears to have misinterpreted the use of the Human Equivalency Concentration (HEC) for the 8-hour and chronic REL derivations. This interspecies dosimetric adjustment provides a rat-to-human ratio for the inhaled caprolactam concentration that occurs at the site of injury, i.e., the epithelial, or mucosal, tissue of the extrathoracic region of the lungs. The extrathoracic region includes the nasal and laryngeal air passages. The HEC approach, in this case, was not used to estimate absorbed systemic dose or toxicity. To clarify how the HEC approach is used, we have included the HEC calculation in the Caprolactam REL Document.

Comment 22: OEHHA employed an additional 100X uncertainty factor. The 100X factor consists of 10X for extrapolation of rodent to humans and 10X for toxicodynamics effects (see Section 8.1 above for criticism of 10X toxicodynamics factor). When OEHHA inappropriately adjusted the inhalation rodent dose to a human equivalent, OEHHA already accounted for adjustment between species. OEHHA utilizes two separate safety factors to account for the same extrapolation (rodent to human).

Response 22: The Human Equivalency Concentration (HEC) adjustment is a dosimetric adjustment to account for the difference in inhaled tissue dose between species at the site of injury in the respiratory tract. Hence, as explained in Section 8.2, no interspecies toxicokinetic uncertainty factor was applied because it was already partially accounted for by the HEC

adjustment, and because the effect is not a systemic effect. However, an interspecies toxicodynamic factor of √10 was applied (see page 48 in the TSD for the Derivation of Noncancer Reference Exposure Levels) to account for the lack of data for differences in response among animal species to the inhaled chemical at the site of injury. In particular, only one comprehensive chronic/subchronic study in one rodent species has been published. It would be helpful and perhaps diminish the uncertainty if other animal species were also assessed at this level of detail for caprolactam inhalation toxicity.

Comment 23: In summary, OEHHA selected the wrong study (13-week rodent inhalation study) for calculation of an 8-hour REL. OEHHA ignored the wealth of human experience including published human studies. OEHHA employed a composite safety factor of 28,659X (23.3 X 12.3 X 100 = 28,659). The proposed 8-hour caprolactam REL is orders of magnitude below levels of caprolactam exposure that are not anticipated to cause adverse health effects in exposed populations.

Response 23: Responses 18 to 22 cover the comments summarized above in Comment 23. However, note that the 23.3-fold factor cannot genuinely be referred to as a safety factor. This so-called factor was a result of applying US EPA benchmark concentration (BMC) methodology to arrive a point of departure for the REL derivation, the benchmark concentration. Following our REL methodology, we did not identify a NOAEL in the subchronic rat study; the Commenter and Reinhold and colleagues apply different criteria to define a NOAEL of 70 mg/m^3 in the study. Applying the BMC methodology to the dose-response data provided a point-of-departure (the 95% upper confidence interval on the dose for a 5% response rate) of 3 mg/m^3. This is the origin of the Commenter's 23.3x factor (70 / 3 = 23.3).

Comment 24: Under the EU Construction Directive, it is recognized that Occupational Exposure Limits (OEL); analogous to ACGIH TLV or NIOSH REL) can serve as the basis of a risk assessment for indoor air quality standards. The EU Construction Directive leads to development of what is referred to as the Lowest Concentration of Interest (LCI). Under EU law, emissions from building materials must be reduced to such a level that assuming long-term occupancy of a room, concentrations in indoor air resulting from such emissions do not pose any threat to the health of sensitive persons even under unfavorable but still realistic assumptions. The procedure for calculating an LCI for a given compound is as follows. The LCI is calculated by dividing the relevant OEL (e.g., German MAK) by a factor of 100 except for irritants. It is clear for the LCI calculation that a safety factor of less than 100 is applicable for irritants. For many potentially carcinogenic substances, the EU employs a 1000X safety factor.

The 2005 and 2008 Health-Related Evaluation Procedure for Volatile Organic Compounds Emissions (VOC and SVOC) from Building Products reports list caprolactam. The LCI value in the 2005 report is 50 $\mu g/m^3$. A 100X safety factor was applied to the applicable occupational standard of 5,000 $\mu g/m^3$. The more recent report issued in 2008 also provides a LCI for caprolactam. The 2008 LCI value is 240 $\mu g/m^3$, an increase of almost 5X compared with the 2005 value. The 2008 LCI calculation employs an approximate 21X safety factor applied to the OEL of 5,000 $\mu g/m^3$.

OEHHA utilized safety factors 29X more conservative than used by EU for carcinogen risk assessments. Based on the information available to both the EU and OEHHA scientists, the 21X safety factor employed by the EU seems realistic and health protective. How OEHHA can justify a 28,659X safety factor for caprolactam, an upper respiratory tract irritant, when a 1,000X factor is used by the EU for carcinogens is not evident and unscientific.

Response 24: OEHHA has reviewed the EU documents cited by the Commenter (i.e., The 2005 and 2008 Health-Related Evaluation Procedure for Volatile Organic Compounds Emissions (VOC and SVOC) from Building Products). The LCI of 50 µg/m^3 cited in the EU 2005 document is based on a German Maximum Allowed Concentration (MAK) of 5000 µg/m^3. The MAKs are "values set at such a level that, according to current knowledge, even repeated and long-term exposure, for up to 8 hours a day within an average 40-hour working week, is generally not expected to adversely affect workers' health over their working lives." The EU 2005 document applies a generic safety factor of 100 to the MAK value, for substances that are not carcinogenic, mutagenic or reprotoxic. This generic safety factor takes into account that following basic differences between conditions in general indoor spaces (such as homes, kindergartens and schools) and those at workplaces:

- Continuous exposure in contrast to a changing and regularly interrupted workplace exposure,
- Existence of risk groups which are not present in the workplace at all (children, senior citizens) or are particularly protected by occupational medicine (pregnant women, allergic persons),
- Lack of exposure measurements and medical checks and, in principle, undefined overall indoor exposure.

The EU 2008 document increases the LCI to 240 µg/m^3 due to "individual substance evaluation". Neither of these documents provides information on how the derivation of caprolactam MAK value of 5000 µg/m^3 and the LCI value of 240 µg/m^3 were performed. It is therefore impossible to compare the procedures used to derived the MAK value with the procedures we have used to derive our REL. However, the EU documents suggest that irritants do not need to adhere to a LCI safety factor of 100. This is presumably why the LCI value was raised from 50 µg/m^3 to 240 µg/m^3 in the EU 2008 document.

It would be helpful to compare the references and derivation used to develop the caprolactam MAK and LCI values. This information does not appear to be easily located using normal search techniques. Without it, OEHHA can only surmise that the MAK suffers from the same weaknesses many other occupational exposure values do (i.e., lack a consistent basis for derivation, may not prevent adverse health effects among workers, do not incorporate recently available data) because they appear to simply use the ACGIH value.

The adjustment used to raise the LCI from 50 to 240 µg/m^3 in the EU 2008 document is cause for concern by OEHHA if irritation was used as the basis for this change. As observed in the Reinhold et al. (1998) study, long-term exposure in rats led to cumulative injury to the cell lining of the nasal and laryngeal airways. Clearly, cellular injury and destruction is different from

acute sensory irritation in which the trigeminal nerves are stimulated by exposure to a chemical irritant, resulting in sensory irritation.

It should also be noted that once exposure duration and tissue dose differences between rat and human are accounted for, OEHHA also applies a safety factor (i.e., uncertainty factor) of 100, similar as that applied in the EU 2005 document. It is misleading to imply that OEHHA is applying a 28,659-fold safety factor when the point of departure is different between the OEHHA REL and the occupational MAK value for caprolactam.

It is also worth noting that EU standards do not apply to the United States or California. Differences in air limit values between the US and European agencies do not often correspond to differences in health risks in the respective population, but rather to different scientific opinions and approaches in setting and enforcing occupational exposure limits.

Comments by Terra Inc. and corresponding replies by OEHHA

B. OEHHA's REL Derivations

Derivation of the Acute Air Reference Exposure Limit (1-hour exposure)

Comment 1: After selecting the right study OEHHA staff has used NOAELs provided in this study incorrectly and the single uncertainty factor they applied may not be necessary for the stated reason listed in this document. For irritation and other actual adverse health effects the NOAEL reported by the authors was 5.0 mg/m^3 and not the 0.5 mg/m^3 selected by OEHHA staff. The only response significantly elevated at this concentration was annoyance to the odor of the chemical. Both the objective measurements (eye blink, eye redness, and nasal resistance) and the subjective symptomology related to the irritant properties of the chemical were not significantly elevated; thus no true irritant response was recorded in this study even at the highest concentration tested. So, if OEHHA considers an UF of 10 is still necessary to assume because asthmatic response to the irritant properties of this chemical have not been tested, then it should be applied to the NOAEL for irritation which was the 5.0 mg.m^3 concentration. This would coincidentally also remove the significant nuisance odor response seen at the highest caprolactam level, a response driven by only a few of the test subjects.

Response 1: Although individual objective measurements and subjective symptomology questions were not statistically significantly elevated ($p<0.05$) at even the highest caprolactam concentration, the total symptom score of 29 acute symptoms was statistically significantly elevated at 5.0 mg/m^3. OEHHA considers this a mild adverse effect appropriate for establishment as the LOAEL. OEHHA considers this a legitimate way to establish a NOAEL/LOAEL because of the large variation in response to individual symptom questions by the relatively few (20 individuals) test subjects. This is a common occurrence in human exposure studies and combining symptoms in effect increases the power of the study.

However, the Commenter suggests that odor alone was solely responsible for increasing the total of 29 symptom scores at 5.0 mg/m^3. It was not clear to us from reading the Zeigler study that this was the case. The 29 individual subjective scores used to determine a total symptom score all relate to sensory perception and irritant qualities of caprolactam, with many scores possibly affected by the perception of odor nuisance. Nevertheless, we have contacted the authors (Dr. Zeigler or Dr. Triebig) to discuss their findings as they relate to OEHHA's acute RELs, and to determine if odor nuisance alone was responsible for the statistically significantly increased total symptom score at 5.0 mg/m^3.

The Commenter also notes that the authors (Ziegler et al.) considered the highest caprolactam concentration of 5 mg/m^3 to be a NOAEL. Ziegler et al. also considered this level of caprolactam to be a LOEL for the most sensitive end point of total symptom score. Their decision that no LOAEL was found is based on other researchers in this field defining an adverse health effect as to cause subjective symptoms with higher gradings of "severe" and "very severe". This score presumably is an averaged score among all subjects. As discussed in our Guidelines (OEHHA, 2005), the endpoint OEHHA uses for determination of a REL, which is intended to protect the health of the community at large, will generally be a mild effect. By our

definition a statistically significant increase in total symptom score, including sensory irritation, odor nuisance, and other general feelings of well-being, qualifies as a mild adverse effect for establishing a LOAEL/NOAEL. However, if OEHHA can obtain the raw data from the Zeigler study, we can make a better determination which individual symptom scores, including odor nuisance, were responsible for increasing the total symptom score.

The Commenter notes that subjective measures of sensory irritation were not statistically significant at $p \leq 0.05$. However, Ziegler et al. did show increasing trends for the objective measures of eye blink frequency and nasal resistance. Unfortunately, the actual p values for these measures were not included in the study. It may be instructive to know what the p values are at the highest caprolactam concentration. We have also asked the primary author (Dr. Ziegler) for this information.

Finally, although OEHHA finds that the total symptom and complaint score is a reasonable for a REL derivation, OEHHA decided that using the increased subjective total symptom and complaint score in which odor annoyance appears to dominate was not as preferable to use as the basis of the acute REL when human sensory irritation data is available. Because there is limited, though adequate, acute sensory irritation data available from the occupational study by Ferguson and Wheeler (1973), we have revised the acute REL based on this study.

Comment 2: While it is standard, accepted regulatory practice to adopt uncertainty factors for those areas where information is limited or lacking, I would point out that it could just as easily be assumed by OEHHA that asthmatics will not be more responsive to the irritant properties of caprolactam. This is based on analogy to the highly reactive and irritant VOC, formaldehyde. A number of well-controlled chamber experiments have been performed on this irritating chemical that show asthmatics exposed incur no adverse impact on their lower respiratory tract as measured by pulmonary function tests (8 references included).

Response 2: The effects of formaldehyde on asthmatics may be dependent on previous, repeated exposure to formaldehyde, particularly in adults. These individuals may have been sensitized immunologically, as in the cases of elevated circulating antibodies, or rendered neurologically hyperresponsive, following repeated or chronic exposures to formaldehyde. Asthmatic responses could be induced with short term formaldehyde exposure in workers occupationally exposed to formaldehyde (Burge et al., 1985; Nordman et al., 1985; Hendrick and Lane, 1977). In contrast, short-term exposure of non-occupationally exposed asthmatics exposed short-term to formaldehyde did not result in an asthmatic response (Sheppard et al., 1984).

There is evidence that children are more susceptible to the adverse effects of chronic exposure. Doctor-diagnosed asthma and chronic bronchitis in children were found to be more prevalent in houses with elevated formaldehyde (Krzyzanowski et al., 1990). This effect was driven by the high disease prevalence observed in homes with kitchen formaldehyde levels >60 ppb, and was especially pronounced among children with concomitant exposure to ETS. This study also indicated that the adverse impacts on children can be as low as 30 ppb. This is compared to the LOAEL of 81 ppb from the studies in adults used as the basis of the chronic REL.

Other studies have supported this finding, while still others presented mixed results. As noted in the OEHHA TSD (OEHHA, 2008), these human studies are not entirely consistent with each other, and there is potential for confounding factors in each. Nevertheless, taken together, they suggest that children may be more sensitive to formaldehyde than adults.

OEHHA also notes that there has been a large increase in the incidence of asthma over the last decades, particularly in children, and thus many people are potentially at risk. Children have higher prevalence rates of asthma than do adults (Mannino et al., 1998). In addition, asthma episodes can be more severe due to the smaller airways of children, and result in more hospitalizations in children, particularly from the ages of 0 to 4 years, than in adults. Thus children, particularly asthmatic children, may be at greater risk from acute exposure to irritants.

The Commenter refers to formaldehyde and the lack of response in asthmatics in chamber studies. In nearly all cases, these studies can only be done on mild to moderate adult asthmatic subjects. There are none to our knowledge that have been conducted on severe child asthmatic subjects.

Although the toxicological endpoint for formaldehyde is eye irritation, the formaldehyde REL must protect against all possible adverse effects. The respiratory irritant effect, with documented potential to exacerbate asthma, is clearly an effect with the potential to differentially impact infants and children. When OEHHA developed the RELs for formaldedhyde (OEHHA, 2008), the toxicodynamic component of the intraspecies uncertainty factor was assigned an increased value of 10 to account for potential asthma exacerbation and applied equally to the formaldehyde acute, 8-hour and chronic REL. These RELs underwent public and peer review and the Scientific Review Panel concurred with the potential increased susceptibility of asthmatic children to formaldehyde.

Adding a 10-fold toxicodynamic intra-individual uncertainty factor for irritant chemicals is a standard procedure for REL development, adopted to fulfill our mandate under SB 25 to ensure our risk assessment procedures are protective of children's health.

Comment 3: As odor is a subjective response to environmental esthetics rather than an adverse health response, it should not alter any individual's ability to respond to either normal daily or emergency situations. Remember that Zeigler et al. (2008) evaluated different subcategories of symptoms. While the total symptom score was significantly different at 5 mg/m^3, those symptoms reflective of irritant complaints and those related to one's sense of well-bring were not significantly different even at this concentration. Further, adopting an uncertainty factor to reduce the potential for odor complaints is not only not needed to protect human health, but it is unlikely to change odor perception in the general population as Zeigler et al. (2008) found the odor ratings for 0.15 and 0.5 mg/m^3 to be the same. The Zeigler study found the odor at the two lower concentrations was only slightly pronounced, and so they concluded, were not to be interpreted as an adverse response.

Response 3: Refer to Response 1 regarding the decision by OEHHA to base the acute REL on the statistically significantly increased total symptom score at 5 mg/m^3. OEHHA did not establish a NOAEL based on odor nuisance at 5 mg/m^3 alone, but rather on the total of 29

subjective acute measures. Increasing trends with increasing concentration were noted for several of the individual symptom questions. We have contacted Dr. Zeigler with regard to the Commenter's assertion that odor alone was responsible for the statistically significant increased total symptom score at 5.0 mg/m^3. Also, note that we have revised the acute REL based on the sensory irritation findings by Ferguson and Wheeler (1973).

We agree with the Zeigler et al. conclusion that, although odor at 0.15 and 0.5 mg/m^3 was statistically significantly elevated ($p<0.01$), the average olfactory odor rating at these two concentrations was about 0.3 (i.e., between "not at all" (0) and "barely" (1) an odor nuisance), and therefore difficult to support as a LOAEL at either concentration.

As noted by the Commenter earlier, the highest caprolactam concentration of 5.0 mg/m^3 resulted in a large score increase ($p<0.001$) to nearly 1.2 (i.e., between barely (1) and "somewhat" (2) an odor nuisance). Zeigler observed that 3 out of 20 individuals (15% of total respondents) considered the odor nuisance to be severe (grade level 4), suggesting that many of the other subjects rated the odor nuisance considerably lower. Such a wide range in response to chemical odor is not unusual among unacclimated human volunteers. Ferguson and Wheeler (1973) also noted considerable variability in response occurred to caprolactam exposure among volunteers.

Given that the 3 subjects recorded odor nuisance as severe at 5 mg/m^3 did not result in immediate need to leave the environment, it is probably not, in itself, the only reason to establish 5 mg/m^3 as a LOAEL. However, the statistically significantly increased total symptom score at 5 mg/m^3 suggests a mild adverse effect, which is an endpoint for determination of a REL in our Guidelines (OEHHA, 2008) in order to protect the health of the community at large. Zeigler's data may also point to a significant subpopulation of individuals that are sensitive to caprolactam exposure (e.g., the 3 subjects that rated odor at 5 mg/m^3 as severe) and indicates that caprolactam exposure causes a general decrease in feeling of well-being.

Comment 4: To set an REL below 0.5 mg/m^3 (500 μg/m^3 or 108 ppb) is overly and unnecessarily conservative given the findings of Zeigler et al. (2008), especially given the fact that this is a one hour exposure limit while all test subjects completed six hours of exposure in this study even when exposed to a 10-fold higher concentration. In contrast, the draft REL derived a 10-fold lower limit of 0.05 mg/m^3, and states that a critical effect being prevented by this exposure guideline is irritation. This is simply not true. OEHHA staff have misrepresented (or misinterpreted) the findings of this study, and then have compounded this mistake by adding a 10-fold safety factor to protect asthmatics in spite of the fact a 10-fold safety factor for irritation was already incorporated into the point of departure concentration they had selected.

Response 4: Ziegler et al. noted that irritant and other symptomology scores increased immediately after entering the chamber containing caprolactam, but then remained at roughly the same levels for the remainder of the 6–hour exposure. This pattern of concentration-dependent irritation is typical of many irritant gases, and caprolactam appears to be no different. The duration of exposure and thus the total dose, within limits, is not relevant to the irritant response. Thus, OEHHA does not make any time adjustments for acute exposure to sensory irritants (i.e., raising the concentration in a concentration-time dependent manner going from 6-hour to 1-hour exposure), as the Commenter seems to suggest we should do.

Also, OEHHA had no intent to misrepresent or misinterpret the findings of Ziegler et al. by suggesting that the acute REL is based only on eye and nasal irritation, as the Commenter suggests. OEHHA states on the page 1 summary of the Caprolactam REL Document that the critical effect is "increased total symptom and complaint score, including nasal and eye irritation." OEHHA considers the entire constellation of 29 subjective questions to be related to the irritant/nuisance effects of caprolactam, including odor, and relevant for establishing a NOAEL and LOAEL. However, OEHHA will re-word the "critical effects" summary to lessen any possible misinterpretation by readers.

Derivation of the 8-Hour and Chronic Reference Exposure Limits

Comment 5: Generally speaking, it is typically assumed that an exposure guideline derived for a particular duration of exposure requires a study of corresponding exposure duration. This fact was apparently the basis for OEHHA ignoring the Zeigler et al. (2008) study completely when developing its 8-hour and chronic exposure RELs. While the Ziegler study exposed individuals to different concentrations for only four days, no adverse health effects were observed and no cumulative effects requiring recovery periods longer than the rest of the day of exposure were indicated by the authors of this study.

Response 5: The Ziegler et al. study exposed the volunteers randomly to three different concentrations of caprolactam (0.15, 0.5 and 5 mg/m^3), and one control exposure over 4 days. The 8-hour and chronic RELs are meant to protect individuals from repeated 8-hr and continuous long-term exposure, respectively, up to a 70-year human life span. The difference in exposure duration between the Ziegler study and the exposure durations for repeated 8-hour and chronic RELs are much too great to consider using the Ziegler study for anything other than an acute REL derivation.

Comment 6: As OEHHA staff conceded the effects of this study were concentration and not time dependent, and Haber's rule does not apply to all chemicals or all irritants. Again formaldehyde is an irritant VOC that is one such example (four references included). So, it is reasonable to argue that the Ziegler study deserves some consideration as a basis for the 8-hour guideline, or to be used as a reality check against the final values derived via other studies, especially animal studies.

Response 6: The 8-hour REL is supposed to be protective against repeated daily eight hour exposures over at least a significant fraction of a lifetime. A 4-day study (in which one day was a control exposure) to study acute effects cannot be considered as a basis for either the 8-hr or chronic REL. The Ziegler study was not designed to assess long-term injury; rather, it was designed to examine the threshold for chemosensory effects in a low concentration range relevant to indoor environmental conditions.

Comment 7: Furthermore, given the other human studies discussed in both the OEHHA document and the Reinhold et al. (1998) subchronic rat study that OEHHA used to derive its chronic REL, it would appear that the 500 $\mu g/m^3$ concentration that was devoid of all irritant and

chemosensory effects seen in Zeigler et al. (2008) is an exposure level that is likely close to one that would also be safe for longer exposure durations like those for the 8-hour and chronic RELs.

Response 7: The reasons for not using the Ziegler study for an 8-hour and chronic REL are outlined in Response 5 and 6. The human studies referred to in our document and the Reinhold study are occupational studies in which caprolactam exposure durations and concentrations and/or descriptions of injury were not well documented. These occupational studies were not designed to adequately examine questions regarding subtle long-term respiratory tract injury. However, given these limitations, the occupational study by Ferguson and Wheeler (1973) suggests that acclimated workers will have no distress in active and semi-active areas at concentrations up to about 7 ppm (32 mg/m^3), but that most unacclimated workers exposed briefly to 10 ppm (46 mg/m^3) will report immediate nasal and throat irritation. For sensitive non-occupationally-exposed individuals, the 7 ppm value will not be protective, and the 10 ppm value is clearly a LOAEL. So it is unclear if any of the occupational study values strongly support even an acute REL of 500 $\mu g/m^3$, let alone an 8-hour or chronic REL, as the Commenter suggests.

Nevertheless, we re-examined the three primary occupational exposure studies (Ferguson and Wheeler, 1973; Billmaier et al., 1992; Kelman, 1986) as suggested by the Commenter and provided a more detailed assessment of the confidence (or lack thereof) we have for any acute and long-term sensory irritation information from these studies. This has resulted in switching the basis of the acute REL (but not the 8-hr and chronic RELs) to Ferguson and Wheeler.

Comment 8: The authors [Reinhold et al., 1998] maintain that effects seen at the lowest concentration represent an adaptive effect that was observed in this laboratory in other studies involving particulate or aerosol exposure. Thus, they conclude it reflected more of an exposure vehicle or physical response to the exposure medium than to the actual irritant properties of the chemical itself. An aerosol delivery system was ostensibly used in this study because a saturated vapor concentration could not achieve the exposure levels desired to be tested in this animal study (i.e., the saturation concentration is stated to be 13 mg/m^3 in Reinhold et al., 1998). So, if the rat responses seen are due to an aerosol exposure, they should not be induced at concentrations below 13 mg/m^3. However, all of the draft RELs are orders of magnitude lower than the saturation concentration, and so, a vapor seems to be the most likely form of exposure individuals will experience at these levels.

Response 8: Reinhold et al. (1998) considered the increased severity of hypertrophy/hyperplasia of goblet cells in the respiratory mucosa and intracytoplasmic eosinophilic material in epithelial cells of the respiratory mucosa to be a localized adaptive response to the minimal irritant effect commonly associated with particulate compounds rather than an adverse toxicological response to the test material in the nasal passages. The authors go on to say that similar responses have been seen in rats exposed to aerosols of mild irritants in other studies conducted at the facility (Huntingdon Life Sciences, Inc.).

However, no positive control was included in this study to support their claim. Also, caprolactam is considered very soluble in water and is hygroscopic, which suggests it can be in a water/particle form in the air. Regardless of whether caprolactam is in particle or vapor form, it

can be expected that the compound will dissolve in the liquid lining of the nasal cavity before reaching the epithelial cells. Therefore, the form in the atmosphere may not be at all relevant to the toxicity. Evidence of a physical form of the compound causing the effect is needed before OEHHA can consider this simply an adaptive effect to the physical form of caprolactam.

Furthermore, hyperplasia of goblet cells and eosinophilic infiltration of the respiratory mucosa are not considered by OEHHA to be merely adaptive responses, but rather are considered adverse effects.

We thank the Commenter for pointing out that the draft RELs and current worker exposure values are below the saturation level of 13 mg/m^3, indicating a predominance of caprolactam in the vapor form. It is more appropriate to use the Regional Gas Deposition Ratio (RGDR) for the HEC adjustment, rather than the Regional Dose Deposition Ratio (RDDR) for particles. We have made this correction in the caprolactam REL document.

Comment 9: In fact, the Zeigler et al. (2008) and Ferguson and Wheeler (1973) are two studies that indicate no irritation in humans occurs even with chronic exposure to the point of departure OEHHA selected (3 mg/m^3). Thus, the additional conversions and uncertainty factors applied to the 8-hour and chronic exposure RELs are not necessary according to OEHHA's own summary of the human studies.

Response 9: Our analysis of the Zeigler et al. study established a NOAEL and a LOAEL of 0.5 and 5 mg/m^3 for statistically significantly increased total sensory and complaint score. Although the point of departure of 3 mg/m^3 that OEHHA determined was based on a subchronic study in rats, and probably not relevant for a comparison with the human acute exposure study by Zeigler et al., the 3 mg/m^3 point of departure value does fall in the range OEHHA considers to be the point of departure for acute human exposure. The Ferguson and Wheeler study examined acclimated caprolactam workers and does not represent the large variability in response of the general population, including sensitive individuals. In addition, the occupational study was mainly examining workers for transient irritant responses to caprolactam and was not designed to examine workers for subtle respiratory tract injuries or deficits from long-term exposure. The available studies are certainly less than would be ideal, and OEHHA would welcome more toxicity studies of this chemical.

Comment 10: OEHHA then further lowers this starting point by assuming Haber's rule should now be applied to irritant effects of caprolactam even though they had previously concluded this rule did not apply to irritation during the derivation of their acute REL.

Response 10: OEHHA did not make a time adjustment for the acute REL because the Ziegler study had collected sensory and complaint data at 1 hour (as well as at 3 and 6 hours of exposure), the exposure duration for the acute REL. Furthermore, Figure 5 in Ziegler et al. shows the total symptom score at each exposure level did not change over the duration of the 6 hour exposures, which is typical of many chemicals that cause acute irritation. However, the higher, longer exposures in rats suggest cumulative injury over time, in that observers noted treatment-related increases in nasal discharge and labored breathing starting the second week of exposure and continuing through exposure cessation at 13 weeks. Thus, a time adjustment was

used to extrapolate to the 8-hour and chronic REL durations. Tissue damage is sometimes loosely referred to as an irritant response but it is not the same thing as trigeminal nerve mediated irritant response (e.g., sensory irritation). Unlike sensory irritation, irritation resulting in tissue damage is likely to be exposure duration dependent as well as concentration dependent. It should be noted that irritant chemicals may cause both sensory irritation and tissue damage, perhaps at a higher concentration.

Comment 11: This [the 8-hour and chronic REL derivation] includes uncertainty factors for the use of subchronic animal data, and two for toxicodynamic considerations. Why two toxicodynamic uncertainty factors are considered applicable given the other corrections made to yield a human equivalent concentration before this cumulative uncertainty factor of 100 was applied is unclear to this reviewer.

Response 11: The Human Equivalency Concentration (HEC) adjustment is a dosimetric adjustment to account for the difference in inhaled concentration between species at the site of injury in the respiratory tract. Hence, no interspecies toxicokinetic uncertainty factor was applied because it was already accounted for by the HEC adjustment and because the injury is at the site of contact and not systemic.
However, an interspecies and intraspecies toxicodynamic factor of $\sqrt{10}$ and 10, respectively, were applied (see page 48 in the TSD for the Derivation of Noncancer Reference Exposure Levels) and are different from each other. The interspecies toxicodynamic UF was applied to account for the lack of data for differences in response among animal species to the inhaled chemical at the site of injury. In particular, only one comprehensive chronic/subchronic study in one rodent species has been published. The intraspecies toxicodynamic factor accounts for the variability in the human population in response to exposure to caprolactam, and accounts for sensitive individuals such as asthmatic children.

Comment 12: One problem with these derivations, and a problem that is frequently seen with other regulatory exposure guidelines, is that the use of animal data by OEHHA has necessitated the use of numerous uncertainty factors which when multiplied together no doubt over-compensate for the uncertainty that is present. Here the final margin of exposure being applied to the original point of departure is so large the final exposure guideline now represents a *de minimis* concentration or daily dose. The original exposure concentration of 24 mg/m^3 is 1,200 times the draft 8-hour REL and 30,000 times the draft chronic REL. Reductions this large seem excessive on face values, but even more so given the fact that a recent human study (Zeigler et al. 2008) found no irritant effects at an exposure concentration (5 mg/m^3) that was just less than 5-fold lower than the LOAEL OEHHA started with (24 mg/m^3) by selecting the Reinhold et al. (1998) study.

Response 12: The cumulative uncertainty factors reflect the uncertainty in extrapolating from animal to human exposure. Regarding use of excessive reduction/uncertainty factors, OEHHA considers 24 mg/m^3 as the LOAEL in the subchronic rat study. Utilizing US EPA Benchmark methodology allows use of the dose-response data to determine a low incidence of effect (e.g., 5% response) about equivalent to a NOAEL, resulting in a point of departure of 3 mg/m^3. In fact, only a total 100-fold uncertainty factor is applied ($\sqrt{10}$ for subchronic to chronic, $\sqrt{10}$ for interspecies toxicodynamic UF, and 10 for intraspecies toxicodynamic UF). Duration exposure

adjustments are used to obtain a REL that is relevant to the duration of exposure for which the REL is protective. US EPA human equivalent concentration methodology is used to obtain a REL that accounts for toxicokinetic differences between rats and humans, respectively. Additional studies in animals and humans could be useful in reducing the total uncertainty factor in this and other RELs. The magnitude of the REL is influenced by a) the toxicity of the chemical and b) the quality of the data. OEHHA agrees with the Commentator that it is fairly standard practice for public health agencies to multiply uncertainty factors.

As noted earlier, the Zeigler acute human study is inadequate as the basis of a REL for long-term exposure (i.e., the 8-hour and chronic RELs). In Response 6 above, a 4-day exposure (in which one day was a control exposure) to study acute effects cannot be considered as a basis for a repeated daily 8-hr exposure or continuous chronic exposure REL. The Ziegler study was not designed to assess long-term injury; rather, it was designed to examine the threshold for chemosensory effects in a low concentration range relevant to indoor environmental conditions.

Comment 13: It is also my understanding that the European Union generates exposure guidelines under its Construction Directive that are designed to be protective of indoor air environments. Its exposure guideline for caprolactam was recently increased to 240 $\mu g/m^3$, a level that is 300-times higher than OEHHA's chronic REL and 120-times higher than its 8-hr REL.

Response 13: OEHHA has reviewed the EU documents (i.e., The 2005 and 2008 Health-Related Evaluation Procedure for Volatile Organic Compounds Emissions (VOC and SVOC) from Building Products) that list caprolactam exposure levels noted by the Commenter. The EU 2008 document increased their Lowest Concentration of Interest (LCI) value from 50 $\mu g/m^3$ to 240 $\mu g/m^3$ due to "individual substance evaluation". The LCI of 50 $\mu g/m^3$ cited in the earlier EU 2005 document is based on a German Maximum Allowed Concentration (MAK) of 5000 $\mu g/m^3$. The MAKs are "values set at such a level that, according to current knowledge, even repeated and long-term exposure, for up to 8 hours a day within an average 40-hour working week, is generally not expected to adversely affect workers' health over their working lives." The EU 2005 document applies a generic safety factor of 100 to the MAK value, for substances that are not carcinogenic, mutagenic or reprotoxic, to generate an LCI of 50 $\mu g/m^3$. This generic safety factor takes into account that following basic differences between conditions in general indoor spaces (such as homes, kindergartens and schools) and those at workplaces:

- Continuous exposure in contrast to a changing and regularly interrupted workplace exposure,
- Existence of risk groups which are not present in the workplace at all (children, senior citizens) or are particularly protected by occupational medicine (pregnant women, allergic persons),
- Lack of exposure measurements and medical checks and, in principle, undefined overall indoor exposure.

OEHHA takes into account all the available data to determine RELs and does not rely on generic safety factors that are not based on actual published toxicity reports for individual chemicals. In addition, the EU documents did not provide information on how the derivation of caprolactam

MAK value of 5000 µg/m^3 and increasing of the LCI value to 240 µg/m^3 were performed. However, the EU documents suggest that irritants do not need to adhere to a LCI safety factor of 100. This is presumably why the LCI value was raised from 50 to 240 µg/m^3 in the EU 2008 document.

It would be helpful to compare the references and derivation method used to develop the caprolactam MAK and LCI values. This information does not appear to be easily located using normal search techniques. Without it, OEHHA can only surmise that the MAK suffers from the same weaknesses many other occupational exposure values do (i.e., lack a consistent basis for derivation, may not prevent adverse health effects among workers, do not incorporate recently available data) because they appear to simply use the ACGIH value.

Even with the deficiencies in the LCI approach, it should also be noted that once exposure duration and tissue dose differences between rat and human are accounted for, OEHHA also applies a safety factor (i.e., uncertainty factor) of 100, similar as that applied in the EU 2005 document.

Comment 14: I would note in Section 3.0 of the OEHHA draft document cites several recent studies of indoor U.S. or California environments that indicate most, if not all, indoor environments, will not meet either the 8-hour or chronic REL. Yet no demonstration of actual adverse health effects occurring at these higher exposure levels is mentioned in the OEHHA document.

Response 14: The chronic and 8-hour RELs are air concentration at or below which adverse health effects would not be expected even in sensitive members of the general population for at least a significant fraction of a lifetime. The threshold at which health effects would occur in the general population is not known and therefore uncertainty factors are applied to a point of departure to help ensure the REL is below a level at which health effects would be seen in the general population. The total uncertainty factors used reflect the type and quality of the toxicity data available for a particular chemical. Under our new guidance, the total uncertainty factor could be as low as 30 fold, or perhaps 10 fold in some instances if good quality human exposure data for a large population that includes sensitive individuals are available (not the case for long-term caprolactam exposure). As the exposure concentration increases above the REL, the likelihood of health effects in the general population increases. However, depending on the unknown level of the population threshold, there may be no adverse health effects at concentrations above the REL. OEHHA's RELs are modified to consider new data as resources permit.

To our knowledge, there are no human toxicity studies demonstrating no adverse effects at concentrations found in California indoor environments. We would happy to consider such studies in our REL development if they exist.

Comment 15: It may be best at present to just promulgate an acute REL following the procedure outlined above, and then delay any determination of a chronic inhalation concentration for lack of an adequate database. This is the approach currently being used by the USEPA, an agency

that has decided that no reasonable RfC concentration for caprolactam can be derived at the present moment because the animal database is inadequate for such purposes.

Response 15: It appears that USEPA has not updated the caprolactam RfC assessment in its IRIS database since 1994, which is prior to the publishing of the Reinhold et al. (1998) subchronic study in rats. OEHHA agrees the database USEPA reviewed in 1994 is too limited to derive a chronic exposure value. USEPA does note in 2001 that significant new studies pertinent to the RfC for caprolactam had been identified in the literature, although no RfC assessment has been conducted yet. Given the comprehensive analysis of the study by Reinhold et al. (1998), OEHHA is confident USEPA will be able to derive an RfC using this study if they choose to conduct an update of their RfC assessment for caprolactam.

Comment 16: [the following comment resulted from a discussion with the stakeholders] During the caprolactam meeting with OEHHA colleagues, rigorous scientific discussions touched upon human studies with both caprolactam and formaldehyde and the topic of objective (e.g., spirometry) versus subjective (e.g., questionnaires) measures of study findings including odor and irritation. The caprolactam REL document discounted human studies with caprolactam and relied upon a rat study for the 8-hour and chronic REL. However, the formaldehyde REL document includes the same type of studies that OEHHA was unwilling to rely upon for the caprolactam REL. This apparent inconsistency was one of the major points of disagreement during our discussions.

Response 16: There is a large body of occupational and non-occupational toxicology studies that examined the long term effects of formaldehyde on humans, many of which were more useful for REL development than the caprolactam studies. OEHHA has reviewed and summarized at least 20 of the best formaldehyde studies in the TSD (OEHHA, 2008), although there are many more in the literature. In contrast, there are only three primary occupational studies in which both caprolactam concentrations were measured and symptoms/signs of exposure were recorded. Unfortunately, these caprolactam studies were not designed well enough for OEHHA to reliably determine a point of departure for chronic exposure.

The three caprolactam studies are summarized first including OEHHA's conclusions, followed by a brief summary of the formaldehyde studies.

Caprolactam Occupational Exposure Studies

1. **Ferguson and Wheeler (1973)**

Five male volunteers were selected. They were "experienced in the work environment" but "relatively unacclimated" - it is unclear what the authors meant by this. Their smoking status was not provided. Subjects were exposed to caprolactam while they were standing or conversing for several minutes downwind from a known emission source (range of 10-100 ppm).

104 ppm eye irritation 1 burning nostrils 5 throat irritation and coughing 5
25 ppm eye irritation 0 burning nostrils 5 throat irritation and coughing 3 (coughing only 1)
14 ppm eye irritation 0 burning nostrils 5 throat irritation 5 (coughing also 1)
10 ppm eye irritation 0 burning nostrils 4 throat irritation 3

The degree of discomfort felt by the workers was considered dose-responsive, but was not quantified due to wide differences in the degree of discomfort between individual subjects. Some of the volunteers were exposed to similar concentrations for up to 30 min, but the sensory effects were not clearly stated or quantified. Brief exposure to 400-1200 ppm caprolactam was described as extremely irritating, resulting in a choking response.

In a second part of the study, approximate 8-hr time-weighted average (TWA) air samples were collected from two locations in a caprolactam polymer facility and one location at a monomer facility. However, the authors said shorter duration samples were also collected for "stress-response test". The conclusion by the authors was that no reported response occurred with exposure to a concentration as high as 7 ppm. This 7 ppm value appears to be derived from Table 1, in which 23 samples of what is assumed to be 8-hr TWA air concentrations of caprolactam vapor were collected over five days in the polymer plant from five different sites of a closed room during working hours. Overall, the caprolactam concentration averaged 3.2 ppm (8-hr TWA range = 1.3 to 6.9 ppm). Time spent in various locations of the closed room was no more than 15 to 45 minutes, but the total time spent in this room was not clear. Table 1 suggests workers could spend up to 30% of their shift in this room.

At a second location in the polymer plant, another 23 samples of presumed 8-hr TWA concentrations were collected on an open floor close to emission sources. The sample were collected from two locations over five days. Overall, the caprolactam concentration averaged 1.1 ppm (8-hr TWA range = <0.5 to 4.5 ppm). The workers reported no response with exposure to a concentration as high as 7 ppm. Time spent in this part of the facility was about 1 to 2 hrs.

At a caprolactam monomer plant, Ferguson and Wheeler (1973) also conducted experimental exposures of worker volunteers and collected 8-hr TWA caprolactam vapor concentrations at various sites over a 3-week period. During experimental exposures no discomfort was noted at concentrations up to 14 ppm at a relative humidity of 100%. The concentration of caprolactam sampled at various worksite locations ranged from 0.2 to 17.6 ppm. Worker exposure durations in the caprolactam-contaminated areas ranged from 10 min to almost 3 hrs. Lack of irritant responses above 10 ppm was thought to be related to the higher relative humidity at the monomer plant, and/or possibly due to more uniform concentrations.

Other than dermal injuries resulting from direct contact to concentrated caprolactam solutions, no general health problems requiring medical follow-up were found in a review of medical records collected during the 18 years of plant operation. In addition, no worker had been removed or asked to be removed from exposure to caprolactam vapor for health reasons during plant operation.

The authors concluded that the response threshold is at or near 10 ppm caprolactam, and that 5 ppm is 50% of the "discomfort" threshold and "somewhat below the no-effect level". The authors also seem to suggest that these brief exposures and a no-effect level of 5 ppm are relevant for long-term occupational exposures, based on no distress in active and semi-active areas of workers to 7 ppm. The 7 ppm value appears to be derived from the highest TWA 8-hr concentration of 6.9 ppm in a part closed room of the polymer plant in which the operator spent 3.3% of his shift (approximately 16 minutes).

OEHHA Conclusion:

To begin with, the authors appeared to be looking for acute responses to caprolactam exposure rather than chronic responses, making it questionable whether this data has any relevance for a chronic REL. The authors' conclusion that 5 ppm is "somewhat below the no-effect level" is not adequately supported by the data. Brief exposure to 10 ppm resulted in nasal and throat irritation in 4 out of 5 unacclimated workers, while possibly just one worker experienced no irritation with a short stay (16 min) in a part of the room with an 8-hour TWA concentration of 6.9 ppm does not present a convincing argument for a no-effect level of 5 ppm. For example, there is not enough information on the actual caprolactam concentration in the room when the worker(s) made their excursions into the workroom. The standard deviation of the caprolactam concentration in the workroom during the 8-hr measurement was not given. The caprolactam air concentration in other parts of the facility that the workers were exposed to was not measured. Because of the potentially highly variable caprolactam concentrations experienced by the workers during their shift, it would have been more appropriate for the workers to wear personal monitors.

The U.S. EPA RfD/RfC Work Group also listed the limitations of the study (USEPA, 1998). The US EPA (as well as OEHHA) notes that significant deficiencies included lack of information on the number of workers and the average duration and distribution of exposure. In addition, no historical air levels are given, smoking history of the workers is not provided, all exposures are determined from area rather than personal samplers, and no attempt was made to reconstruct individual exposure histories.

At best, the few-minute exposure of five unacclimated workers to 10 ppm (46 mg/m^3) can be used as a LOAEL for acute exposure. OEHHA derived an acute REL based on this finding for comparison to the acute REL derived from the human chamber study by Ziegler et al. (2008).

2. Kelman (1986)

Kelman (1986) conducted a clinical and occupational history of eight workers, seven of which were smokers, at a Nylon 6 manufacturing plant. Exposure was described as caprolactam vapor from heat-curing ovens, which subsequently condensed into a fume in the workplace air. Contact of the fume with cooler surfaces resulted in the formation of light feathery flakes. Average worker exposure was 4.8 years (range 9 months to 13 years) and mean atmospheric caprolactam dust concentrations at the time of the study were 84 mg/m^3 (range 22-168 mg/m^3) for static samplers and 68 mg/m^3 (range 6-131 mg/m^3) for personal samplers. The caprolactam dose and exposure durations for individual workers were not provided. Recovery of caprolactam vapor from distilled-water bubblers was considered negligible, which the authors interpreted as indicating exposure was limited to caprolactam dust.

Kelman (1986) reported that several of the workers (number not given) complained of “some degree” of eye, nose, and throat irritation. It was unclear from the study if the irritation was chronic in nature. All but one reported peeling of the skin on the hands. Five workers showed abnormal maximal expiratory flow volumes. However, the author considered the lung function tests unremarkable when the smoking history of the workers was taken into account. Blood and

urine samples were collected for assessment of hematological, hepatic and renal functions. No evidence of systemic toxicity was found.

OEHHA Conclusion:

At best, a LOAEL of 68 mg caprolactam dust/m^3 is observed, but is inadequate as a chronic REL point of departure. No historical air levels are given and no attempt was made to reconstruct individual histories of worker complaints and caprolactam exposure. A confounding factor is that 7 of 8 workers examined were smokers. Also, it is already established from the Ferguson and Wheeler study that acute exposure to the lower concentration of 46 mg/m^3 (10 ppm) results in nasal and throat irritation, although caprolactam was reportedly in vapor form.

3. **Billmaier et al. (1992)**

Billmaier et al. conducted an industrial exposure study of selected workers in two caprolactam plants, Chesterfield and Hopewell. Forty-nine workers were selected (27 smokers/ex-smokers) with 63 controls (workers not working in caprolactam areas, 42 smokers). The controls were matched to the exposed workers (all males) for age, race and smoking status. The workers selected had an average work exposure of 18.7 years (range 8.2-31.7 years) against matched controls. The level of caprolactam in the work areas was determined occasionally by historical industrial monitoring over the previous 10 years. The average concentrations from past monitoring in the Chesterfield plant were an average of 4.5 mg/m^3 (1.0 ppm) in the "Polymer 25" area and 9.9 mg/m^3 in the "Spinning 26" area. Short term measurements of 15-59 minutes during specific plant operations that represented maximum short-term exposures to caprolactam vapor ranged up to 34.8 mg/m^3. For the Hopewell plant, the levels were 4.2-7.8 mg/m^3 from past monitoring and an average of 17 mg/m^3 (3.7 ppm) with a range of 2.3-30.8 mg/m^3 (0.5 to 6.7 ppm) from short term measurements.

Pulmonary function tests were obtained for all exposed and control workers. Pulmonary function tests began in 1978. "Nurses notes" were not used for Chesterfield workers to look for reports of any illness. These notes were obtained from workers who were ill, injured, had a physical examination or a return to work examination, or others over a period of 11 years. Only a few episodes of injury or illness were noted in the medical records that were specifically related to caprolactam exposure. One employee reported dermatitis on two separate occasions, and another employee reported dermal irritation following direct exposure to a lactam-containing solution. A third employee complained of eye irritation on one occasion and reportedly inhaled partially polymerized nylon flakes on another occasion, leading to nausea. No specific caprolactam exposure-related nose or throat symptomatology was reported. However, "symptoms" recorded in the notes may not have been done as this was optional.

There were no significant differences between exposed workers and their controls in the pulmonary function tests or lung function over the years. Wide differences were shown in the initial (using a Collins Eagle spirometer from 1980 to 1988) and last (using a Puritan Bennet spirometer which replaced the Collins Eagle spirometer) FEV_1/FVC ratios between smokers (n=21), ex-smokers (n=12) and non-smokers (n=7) but not between smokers and controls. The authors concluded that if there were adverse effects of caprolactam exposure on lung function,

there should have been differences in the FEV_1/FVC ratios between the exposed workers and the controls.

OEHHA Conclusion:

OEHHA notes several uncertainties with the Billmaier et al. (1992) study that preclude it from use as the basis of a chronic REL. A measurable decrease in lung function generally requires a larger sample population of exposed and control workers. Difference in the FEV_1/FVC ratios in smokers, ex-smokers and non-smokers may be due to the fact that tobacco smoke is inhaled deeply whereas caprolactam may not be. Smokers could be heavy smokers, and they could smoke at work and during non-working hours whereas caprolactam exposure would occur largely at work. Other toxicological studies summarized in this document indicate the main endpoint for caprolactam exposure is the upper respiratory tract. Thus, FEV_1/FVC ratios may be an ineffective method to measure caprolactam effects. U.S. EPA (1998) also notes that the spirometry performed was not in accordance with current guidelines and quality assurance procedures.

Another weakness is that individual worker exposure histories could not be clearly determined due to high variability in caprolactam levels and changes in job responsibilities throughout the workday. As noted earlier, the irritation data from "nurses notes" are probably unreliable. Finally, the authors did not conduct a survey of the workers regarding sensory irritation symptoms or examine the upper respiratory tract for signs of inflammation. The lack of evaluation of the relationship between exposure concentration and sensory effects precludes this study from use to derive an acute REL. Inadequate examination for any chronic effects of caprolactam exposure precludes this study use to derive a chronic REL.

Formaldehyde Occupational and Exposure Studies

The basis of the chronic REL for formaldehyde exposure is the study by Wilhelmsson and Holmstrom (1992). The author observed increased nasal obstruction and discharge, and frequency of cough, wheezing and symptoms of bronchitis in 66 formaldehyde workers exposed for 1-36 years (mean = 10 yrs) to a mean concentration of 0.21 ppm formaldehyde. All workers were exposed almost exclusively to formaldehyde, the concentrations of which were measured with personal sampling monitors. Referents consisted of 36 office workers with exposure to a mean concentration of 0.07 ppm formaldehyde. Symptom data was collected by questionnaire.

This study is supported by the findings of Edling et al. (1988), which found histopathological changes in nasal mucosa of workers (n=75), collected by nasal biopsy, exposed to formaldehyde concentrations of 0.08-0.89 ppm for an average of 10.5 yrs (range 1-39 yrs).

Note that only one of the three caprolactam studies had a referent control exposure group, only one of the three caprolactam studies used personal monitors, none of the caprolactam studies took nasal biopsies for histological examination, and none provided adequate symptom questionnaires to the exposed workers.

Below is a table of the formaldehyde studies and their findings that are discussed in the TSD. Although some individual studies were not ideal for development of a REL on their own, the sheer number of studies that show similar effects in the same concentration range as that found in the primary studies strongly supports the development of a REL for formaldehyde.

Formaldehyde Occupational and Exposure Studies in Humans

Study	**Endpoint**	**NOAEL**	**LOAEL**
Wilhelmsson and Holmstrom, 1992	nasal obstruction & discharge, cough, wheezing, symptoms of bronchitis	0.07 ppm	0.21 ppm
Edling et al.,1988	Histopath changes from nasal biopsies	Presumed about 0 ppm	0.08 – 0.89 ppm
Boysen et al., 1990	Histopath changes from nasal biopsies	Presumed about 0 ppm	0.5- > 2 ppm
Grammer et al., 1990	Eye irritation	-	0.003 – 0.073 ppm
Kerfoot & Mooney, 1975	Eye & upper resp irritation	-	Begin at 0.25 – 1.39 ppm
Ritchie & Lehnen, 1987	Sensory irritation	-	Begin at 0.1 ppm
Liu et al., 1991	Respiratory & allergy exacerbation	-	Begin at 0.09 ppm
Olsen & Dossing, 1982	Sensory irritation	0.05 ppm	0.29 ppm
Broder et al., 1988	Eye & upper resp irritation	0.035 ppm	0.043 ppm
Alexandersson & Hedenstierma, 1989	Decreased FVC, FEV_1, FEF_{25-75}	-	0.4 – 0.5 ppm
Kriebel et al., 2001	Eye, nose,& throat irritation, decreased PEF	Own controls	0.70 ppm
Kilburn et al.,1989	Reduced FVC, FEV_1, $FEF_{25-75,}$ & FEF_{75-85}	Presumed about 0 ppm	0.2-1.9 ppm
Malaka &	Resp. irritation,	0 ppm	<5ppm & >5

Study	**Endpoint**	**NOAEL**	**LOAEL**
Kodama, 1990	resduced FEV_1, FEV_1/FVC , FEF_{25-75}		ppm groups
Srivastava et al., 1992	Increased resp & systemic problems, increased formic acid in urine, abnormal chest x-rays	Presumed about 0 ppm	0.025 ppm
Study	**Endpoint**	**NOAEL**	**LOAEL**
Holmstrom & Wilhelmsson, 1988	Eye, nose & deep airway irritation, diminished olfactory ability, delayed mucociliary clearance & decreased FVC	Presumed about 0 ppm	0.17 ppm
Alexandersson et al., 1982	Eye & throat irritation, airway obstruction, decreased FEV_1, FEV_1/FVC, & MMF		0.36 ppm
Horvath et al., 1988	Sensory irritation, changed FEV_1, FEV_1/FVC, FEF_{25}, FEF_{50}, & FEF_{75}	0.05 ppm	0.69 ppm
Gorski & Krakowiak, 1991	FEV_1, FVC, PEF, IgE	$\leq$ 0.5 ppm	No effect
Alexandersson & Hedenstierna, 1988	Increased eye, nose & throat irritation, decreased FVC & FEV_1	Presumed about 0 ppm	0.33 ppm (0.11-2.12 ppm)